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CERTAIN ASPECTS OF PRACTICAL ENDOCRINOLOGY*

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With the increasing understanding of the function of the several glands of internal secretion, and with the availability of potent extracts and preparations from these endocrine glands, the clinical laboratory is being asked more frequently to perform tests for glandular dysfunction, and to test the efficacy of hormone treatment. The endocrine glands form definite chemical substances, hormones, which are secreted directly into the blood stream, and bring about physiological responses in other organs and tissues to which they may be carried. It is the purpose of this paper to outline for you, briefly, some of the laboratory procedures which you may be called upon to employ in the assistance of endocrine diagnosis.

Generally acceptable, and physiologically workable theories as to the mode of action of most of the glands of internal secretion have been suggested. These theories have been worked out from both experimental and clinical data. In the laboratory, extirpation experiments, gland transplantations, and the treatment of both normal

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animals, and animals from which the gland under study has been removed, with potent hormone extracts have contributed information. Other data have been obtained from the recognition of certain clinical syndromes; known from autopsy, biopsy, surgical, therapeutic, and other signs to be the result of certain glandular dysfunctions. By these means it is well recognized that certain changes in normal bodily function result from abnormal action of the thyroid, pancreas islet tissue, parathyroid glands, certain phases of hypophyseal function, adrenal cortex, and gonads. In many of these conditions, clinical tests can very easily serve, when coupled with the general symptomology, as diagnostic criteria in the identification of the particular pathology. The various tests for faulty thyroid action, and for diabetes mellitus are good examples of such specific laboratory procedures. On the other hand, clinical tests for faulty hypophyseal action are very difficult inasmuch as the hypophysis acts, in the great majority of its suggested roles, not by direct action upon body tissues or functions, but through the intermediate action of other endocrine glands—which may be either stimulated or inhibited. Recently, with the availability of adrenal cortical hormone and ovarian hormones, much interest has been shown in methods which may aid in the diagnosis of adrenal cortex, and ovarian, dysfunction, in which therapy with the active hormone extracts might be expected to be of clinical benefit. The several laboratory procedures which will be discussed here are those which are suggested as particularly useful in the differentiation of adrenal cortical dysfunction, and ovarian abnormalities, from similar conditions which are, however, of non-endocrine origin.

In order to obtain a better insight into the rationale for, and the significance of, the several tests which will be mentioned it may not be out of place to outline briefly the probable physiological functions of the adrenal cortex, and of the ovary, and to point out what changes follow the extirpation of these glands in the laboratory animals, or result from clinical hypo-function.

Adrenal Cortex—The adrenal cortex, which forms the outer "rind" of the adrenal gland, is now known to be one of the endocrine glands essential to the life of the animal. Upon the complete extirpation of both adrenal glands the experimental animals die within 5 to 20 days—there being some species difference in the

response to adrenalectomy. The general symptoms of adrenal insufficiency are,—loss of appetite, possibly accompanied by loss in weight, asthenia, lethargy, and, usually, lowered body temperature. The blood findings in acute adrenal insufficiency are well known, and are shown also in clinical hypo-adrenia, although in many instances of sub-acute insufficiency the changes are not marked. These changes include increased non-protein-nitrogens and urea, increased blood potassium, decreased sodium chloride, hemo-concentration, lowered blood volume as a result of the hemo-concentration, and lowered blood pressure and decreased blood flow as a result of the lower blood volume, and, depending upon the species of the animal, varying degrees of hypoglycemia—particularly in the terminal stages. Several theories have been advances as to the primary function of the adrenal cortex, and no detailed discussion seems necessary here, inasmuch as the work is well covered in review journals and in the original papers. It seems, however, possible to say that the probable function of the adrenal cortical hormone is to regulate and maintain the normal water and electrolyte balance, with a possible secondary involvement of carbohydrate and lipid metabolism.

Acute adrenal cortical failure in humans was first reported by Addison in 1855, and the condition, not a common syndrome, is known as Addison's disease. Its clinical recognition is made easier by the presence, in a large proportion of the cases, of definite and characteristic changes in the pigmentation of the skin, in addition to the clinical findings outlined in the previous paragraph. In the cases of sub-acute, or mild, hypo-adrenia these clinical symptoms are not so marked, and the increased pigmentation seldom occurs. It is in the separation of such cases which are due to adrenal cortical involvement, from those in which the asthenic signs are due to other causes that the laboratory can give the greatest aid in diagnosis.

The symptoms of acute adrenal insufficiency are characteristic, and so easily recognized that Harrop and his co-workers (2) proposed that a patient might be thrown into an acute Addisonian crisis as a diagnostic test for sub-acute adrenal cortical insufficiency. The patient is placed on a diet very low in sodium chloride, and the lowered salt intake, coupled with the already present failure of the

sodium chloride regulating mechanism, produces a typical Addisonian crisis in a patient who was suffering from a sub-acute insufficiency. The condition may be further aggravated by the addition of potassium to the diet. The induction of an Addisonian crisis as an index of adrenal insufficiency has, however, a certain element of danger. Fatal results of this test have been reported (3), and the test should never be done except under carefully controlled conditions and where adequate amounts of adrenal cortical hormone are instantly available to combat a possible serious attack of adrenal insufficiency.

Zwemer and his co-workers (8) have proposed the so-called potassium tolerance test as a measure of adrenal cortical function. This test is very sensitive in their hands, and consists essentially in determining the blood potassium at frequent intervals following a test dose of potassium. The normal individual will show little if any change in blood potassium following such a test dose, whereas the patient having faulty adrenal cortical function will show a rapid rise in potassium which remains at the higher level for several hours before returning to normal. The analytical methods have been improved by Zwemer and Truzskowski (6, 7) but because of the time involved, and the special apparatus and reagents necessary, the potassium tolerance test remains a technique which the routine laboratory is not ordinarily equipped to perform. The determination of the Schneider index, a general fitness test, has been used in some laboratories as a measure of adrenal cortical efficiency, but it does not seem to be sufficiently specific as a sole means of diagnosis in adrenal dysfunction.

Cutler, Power, and Wilder (1) have recently reported a method for the differential diagnosis of adrenal insufficiency which seems to fill the requirements for specificity, ease of laboratory procedures, and comparative safety in determination. In their paper they describe quite completely the technique and its repetition seems needless here. The test is based on the phenomenon that the ingestion of potassium will, in the adrenalectomized animal, or in the patient suffiering from adrenal insufficiency, result in an increased urinary excretion of sodium chloride. In the normal individual little change in urine sodium chloride occurs following similar treatment. The test consists of the determination of the amount of sodium and/or

chloride excreted during a four-hour period on the third day of the dietary regime,—forming the basic conditions of the test,—which is well explained in the original paper. Inasmuch as the sodium and chloride excretions parallel each other, it is sufficient to determine the urinary chlorides—an easy and familiar laboratory procedure. The authors claim that by this method no confusion results from an overlap of normal and pathological values, and that it is possible to distinguish between conditions of hypo-adrenia and other similar appearing symptomologies. It would seem that this method is the best, and most easily available for the differential diagnosis of adrenal cortical insufficiency.

Ovarian Function—Only recently has any effort been made to make a definite diagnosis in ovarian disorders, or to follow by critical, objective, laboratory means the results of therapy with the ovarian hormones. With the better understanding of the normal events and changes in the female reproductive system during the various phases of the sex cycle has come the realization that it is possible to check the efficiency of the ovarian function in women, as well as in the common laboratory animal.

A brief outline and discussion of the normal female cycle, and the role of the hormones in this cycle, may serve as an aid in the interpretation of the various tests which are useful in the study of ovarian physiology. It is well known that the female gonad, the ovary, produces, in addition to the germ cells, two classes of hormones upon which the normal sex development and cyclic function depend. One group, the so-called follicular hormones, are produced in larger amounts during that part of the cycle in which the Graffian follicles are enlarging, and the ova are maturing. At the time of ovulation these follicles rupture, the ova are extruded, and at the sites of these ruptures, scar tissue forms. This scar tissue is, however, of a glandular nature and is called the corpus luteum. This tissue forms a hormone, the corpus luteum hormone, of which more will be said later. As the time for the beginning of the next cycle approaches, the secretory activity of the corpus luteum probably decreases, and there is a gradual increase once more in the amount of follicular hormone being formed as the next ova start to mature. Thus it can be seen two types of ovarian hormones, the follicular

hormones and the corpus luteum, play synergistic roles in the maintainance and regulation of the normal sex rhythm in the female. These two types of hormones are *not* antagonistic, as was at one time supposed, but for the proper action of the corpus luteum hormone the sex organs must have first been prepared by the adequate action of the follicular hormones.

One function of these hormones is to condition and regulate the proper development of the secondary sex characteristics of the individual, but the most important function is to prepare the uterus for the implantation of the fertilized ova, and to maintain intrauterine conditions which are compatible with the continuation of pregnancy. In the lower animals the action of the follicular hormones also insures, to some extent, that fertilization will take place, by bringing about a so-called "heat period," or *estrus* period, at about the time of ovulation. During estrus, mating will occur and optimum conditions for fertilization are present. The period of estrus is characteristic of the sex cycles of the lower mammals, and gives to the cycle the name—*estrus cycle*—and because of the role of the follicular hormones in bringing about this heat period they are called *estrogenic hormones.* This terminology will be used hereafter in speaking of the "follicular hormones." Following the action of the estrogenic hormones in bringing about proliferation of the uterine lining, the *endometrium,* the corpus luteum acts upon this tissue to produce still further changes, i.e., some additional thickening, increased vascularization, and growth of endometrial glands. These latter changes, which are the final stages in the preparation of the uterine lining for implantation, are spoken of as "progestational changes," and the corpus luteum hormone is properly termed *progesterone.* If fertilization and implantation do not occur, the endometrium returns to the resting stage until the next cycle. In the animals having estrus cycles this process is one of regression, with some desquamation, but with no endometrial bleeding. In the primates, however, this progestational membrane is sloughed off, and considerable endometrial bleeding occurs. This is the phenomenon known as menstruation, which is characteristic of the primate cycle, and from the start of which, times during the cycle are usually calculated.

It must be brought out here, that although the estrus cycle and

the menstrual cycle are characteristically identified by different physiological phenomenon, which are not comparable, the changes occurring in the reproductive system, in the ovary, uterus, and vagina, are comparable and the knowedge gained from the study of the shorter, more conveniently investigated estrus cycle can be shown to be true for the menstrual cycle of the primates. The characteristic effects of the two ovarian hormones, estrogenic hormone and progesterone, upon the uterine endometrium, and upon the other sex organs is qualitatively the same in both types of cycles. This may be made clearer by a study of Figure 1, particularly parts A, B, and C.

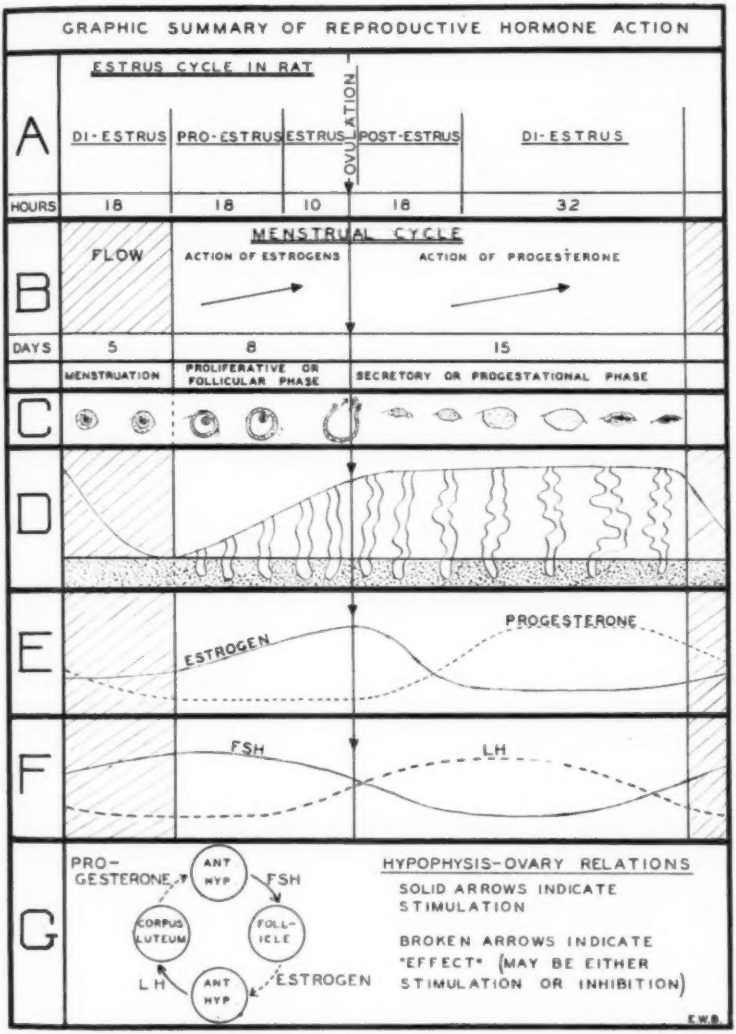
As is well known, it is possible to follow the course of events during the estrus cycle by an examination of the cell picture shown by vaginal smears. Under the influence of the estrogenic hormones the smear cell picture changes from the resting, or diestrus stage, in which the smear is made up largely of leucocytes, with an occasional epithelial cell; through the proestrus condition during which the nucleated epithelial cells gradually replace the leucocytes; to the estrus stage in which the smears show practically 100% cornified cells, with few, if any, nucleated epithelial cells, and no leucocytes. This cornification gradually disappears during post-estrus with an infiltration of leucocytes, until the smear characteristic of diestrus is again reached. The vaginal smear technique has two principal uses: It serves as a method of following the cycle in normal animals, and it also serves as an assay method in the determination of the potency of estrogenic preparations. In the latter instance, castrate females are used and in these animals, due to the removal of the ovaries, and the loss of the action of the ovarian hormones, the reproductive organs remain in a castrate condition. During this time the vaginal smear picture is that characteristic of the resting, or diestrus, stage. If, to these castrate females, a potent estrogenic hormone is administered, the vaginal smear will change to that typical of estrus, indicating that the animal has been brought into "heat," or estrus, by the hormone preparation. This test forms the basis of the generally accepted unit of estrogenic potency, the "rat unit," which is defined as, "the least amount of hormone which, when injected in three divided doses, at four-hour intervals, to a group of at least 20 castrate female rats, weighing between 120 and 160 grams, will produce

an estrus type smear in at least 75% of the rats so treated." A description of the vaginal smear technique, as well as photomicrographs of typical smears, appear in all text-books of endocrinology and will not be described in detail here.

Just as the estrogenic hormones produce estrus in the lower animals, as shown by vaginal cornification, they produce comparable changes in the reproductive system of the human female, and here these changes may also be followed by vaginal smears as has been shown by Papanicolaou and Shorr (5). The stage of the human cycle comparable to the estrus stage of the rat is termed the proliferative or "follicular" phase, due to the growth of the endometrium under the influence of the estrogenic hormone. During this period there is considerable growth and thickening of the endometrium. Following ovulation further thickening of the uterine lining occurs, and in addition marked growth and differentiation of the uterine glands accompanied by increased vascularization, due to the action of the progesterone secreted by the enlarging corpus luteum. This latter stage is spoken of as the secretory or progestational phase. The relationships between follicular growth, ovulation, development of the corpus luteum, uterine endometrium changes, and estrogenic hormone and progesterone secretion are also shown in Figure 1, particularly in sections C, D, and E. As can be seen from this chart the menstrual flow begins shortly after the progesterone secretion starts to decrease and after the estrogen secretion has begun to increase. It has been suggested that the sloughing of the progestational membrane, with the accompanying bleeding may be due to either the decrease of the progesterone below the critical level necessary for the maintenance of the endometrium, or to the simultaneous decrease in progesterone and increase in estrogen—giving a ratio of progesterone to estrogen which is lower than the critical level at which the progestation endometrium can be maintained. In the first instance menstruation would be due to lack of progesterone; in the second instance the estrogenic hormone would act as a positive agent in the endometrial sloughing. It would be this second theory which would furnish a rational for the use of estrogenic therapy in conditions of amenorrhea.

Papanicolaou and Shorr (5) have described the technique of doing vaginal smears on humans, and they suggest that it be used

FIGURE I



(Over)

FIGURE I. EXPLANATION OF CHARTS

A. Represents the approximate chronological sequence of stages in the rat estrus cycle. Charted so that ovulation time coincides with that of the menstrual cycle shown in "B".

B. Represents the approximate chronological sequences of stages in the human menstrual cycle. The cycle is started with the beginning of the menstrual flow. The same time relationships hold in the other charts, C to F.

C. Gives a diagrammatic picture of the gradual development of the follicle up to the time of ovulation, and the development of the functional corpus luteum and its degeneration.

D. Illustrates, diagrammatically, the growth of the uterine endometrium during the cycle. During the "follicular phase" the endometrium proliferates, but there is little development of the endometrial glands. During the secretory, or progestational phase, there is some further thickening, but the principal changes are the growth, and modification of the uterine glands and increased vascularization. These changes are conditioned by the secretion of proper amounts of estrogenic hormone and progesterone during the respective phases of the cycle. The thickened, progestational endometrium, is sloughed during the menstrual flow down to the basic epithelial layers, represented by the stippled area.

E. Shows the approximate relationship, in time and in the relative amounts secreted, between the estrogenic hormone and progesterone.

F. Illustrates the probable time and relative quantities of hypophyseal gonadotropic hormones, FSH (Follicular stimulating hormone), and LH (Luteinizing hormone) secreted by the hypophysis during the cycle. This chart together with chart "E" will show the approximate relationships between the hypophyseal and ovarian hormones.

G. Summarizes the ovarian-hypophyseal relationships, and indicates that this effect is a reciprocal one.

as a method of differential diagnosis in determining whether ovarian dysfunction is actually present in a particular case or if the symptoms are due to other organic disturbances. If during menstrual cycles the patient shows no smears which are normal for the follicuar phase, it might be safely assumed that there exists some hypofunction of the ovary in the secretion of estrogenic hormone, and that estrogenic therapy might be expected to be of some benefit. If the follicular phase of the cycle is abnormal, it follows, in the light of the previous discussion, that the progestational phase will also be atypical and the flow at the next menstrual period will be from a non-progestational type of endometrium. In the case of menopause disorders, following the decrease in ovarian hormone activity, the smear usually shows a picture characteristic of the menopause, and closely approximating that of the castrate rat. This smear is present in artificial as well as natural menopause. When estrogenic therapy is instituted it is possible to follow the course of the treatment by examining the smears at frequent intervals, and by this means the doctor is able to regulate the dosage to bring about the desired effect. It seems that the use of vaginal smears in humans, and the proper interpretation of such smears, furnish the most valuable technique available to the clinician through the laboratory for the differential diagnosis of ovarian dysfunction, and for the objective observation of the progress of estrogenic therapy. As has been pointed out by Papanicolaou and Shorr it is possible to permit the patient to take her own smears at frequent intervals, and to bring them to the laboratory at the time of the reguar check-up.

In addition to the vaginal smear technique two other laboratory procedures are of value in the determination of the efficiency of ovarian hormone action during the cycle. The first, and most important is the taking of endometrial biopsies. As a matter of fact this technique probably tells more about the patient's hormone balance than any other, but it is, unfortunately, a technique in which the average patient may not be overly cooperative. As far as laboratory procedure is concerned this method involves no new technique; the biopsy specimens being fixed, stained and mounted in the usual way. The last method which will be mentioned by which the ovarian hormone balance may be checked is by the determination of the sex hormones excreted in the urine. This method, though

extremely valuable from the research standpoint, is not adapted to routine laboratory use as it involves carefully controlled hydrolysis of the urine, complete extraction of the urine with organic solvents, a certain degree of chemical purification, and finally the assay of the amount of estrogenic hormone obtained by either a colorimetric method, which is none too accurate, or by bio-assay on castrate rats, as described above. As a rule, where such research is being carried out by any group in a hospital, these special techniques will be turned over to special research assistants, and will not be handed over to the routine laboratory.

From the therapeutic standpoint the estrogenic hormones are by far the more important of the ovarian hormones. Progesterone, while available, is still quite expensive, and although its use has been suggested in certain abnormal conditions of the female reproductive cycle, the therapy of choice is usually the estrogens.

Ovarian-Hypophyseal Relationships—To complete the picture some word should perhaps be said in connection with the close physiological relationship between the ovary and the hypophysis. It is well known that hormones secreted by the anterior lobe of the hypophysis control, to a large extent, the functioning of the ovary. This holds true in both the follicular phase and the progestational phase of the menstrual cycle. The reverse relationship also obtains, i.e., the secretions of the ovary condition the functioning of the hypophysis. The fact that this interglandular relationship is a reciprocal one has led many research workers and clinicians to suggest that the ideal way to treat hormone imbalances of the female reproductive system would be by cyclic therapy with estrogens followed by progesterone, simulating the conditions present in the normal cycle. Not only would this type of treatment more normally replace the faulty ovarian function, but it would, at the same time, expose the hypophysis to a more normal hormone environment than if either the estrogens or progesterone were given alone.

As is known the hypophysis secretes at least two gonadotropic hormones; the follicular stimulating hormone, FSH, and the luteinizing hormone, LH. The FSH stimulates the ovary to develop follicles and to secrete estrogenic hormone. As the level of the estrogenic hormone gradually increases the pituitary, (whether by

stimulation or inhibition makes little difference), stops secreting FSH and starts to produce LH. By the time of ovulation, therefore, the pituitary is secreting considerable amounts of LH which will stimulate the ovary to produce functional corpora lutea, and to secrete progesterone. By the time the latter part of cycle has been reached, just prior to menstruation, the hypophysis, conditioned by the progesterone being secreted, has stopped making LH, and is once again secreting FSH in preparation for the next cycle. These reciprocal relationships can be seen in sections E, F, and G of Figure 1.

It is unfortunately true, that dysfunction of the gonadotropic rhythm of the anterior lobe of the hypophysis, may be the fundamental factor in a hormone unbalance the observable symptoms of which may be typical of ovarian dysfunction, and it may be impossible to say that the hypophysis is at fault. Fortunately, however, the symptoms, being those of ovarian upset, may be completely relieved by ovarian hormone therapy alone, and it might even be hoped that, inasmuch as the ovarian-hypophyseal relationship is a reciprocal one, the treatment with the estrogen, progesterone, or both may actually act as the initiating stimulus to a reestablishment of the normal conditions indicated in Figure 1, G. It is hoped that, before long, adequately purified preparations of FSH and LH will be generally available, at which time it may be possible to use the gonadotropic hormones somewhat more successfully than seems to be possible at the present time.

Perhaps the medical technologist should feel glad that no elaborate tests for anterior lobe function have come into use. The time may not be far distant, however, when even the medium-sized hospital may require a technologist specially trained in the techniques necessary for the differential diagnosis of endocrine disorders.

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STUDIES IN EXPERIMENTAL DEHYDRATION*

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Introduction

When the amount of water ingested by the body is greatly diminished, or when the amount excreted is much greater than the intake, or when water is lost in large amounts in any manner, a state of dehydration of the body results. This is a frequent clinical finding in diarrhea, alimentary obstruction, persistent vomiting, intestinal intoxication, terminal nephritis, and in the acidosis of diabetes and other pathological states. The condition varies somewhat depending on the causitive factors and on the degree of dehydration. Anhydremia is the first effect, sudden withdrawal of water resulting in immediate concentration of the blood as shown by increase in the serum proteins, red count and hematocrit readings, and by a decrease in the blood volume (1).

The body possesses an available supply of water in the various tissues. Muscle is the most important reserve of the body, containing about half the body water, while skin contains one fifth and blood seven per cent (2). These water reservoirs can be drawn upon before any considerable degree of dessication occurs. Stored body fat and glycogen are utilized when dehydration is accompanied by starvation, and finally there is some destruction of the body proteins. The secretion of urine is greatly decreased, severe cases resulting in complete anuria. There is evidence of impaired function of the kidneys, and sometimes acidosis develops, due to the acumulation of acids which are normally excreted. There is always considerable loss of body weight.

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Gamble (3) states that in progressive dehydration there is extensive withdrawal of interstitial fluid, and the blood volume is maintained for long periods by the water and sodium and chlorine ions derived from this fluid. He notes a slight loss of water from the tissues, while cell water seems to be maintained (4). Dehydration of the plasma alone is enough to cause death. Drake, McKhann and Gamble (5) found that the per cent of water and chlorides in skin, tissues, blood and total body remained the same in rats dehydrated by means of pyloric obstruction, and in a control rat deprived of food and water. These authors regard the water lost as a waste product of the consumption of body fat, glycogen and protoplasm. This water loss, they conclude, is accompanied by a parallel loss of solids.

The present knowledge of the state of the body after water deprivation is far from complete. Kramár has described the symptoms of experimental dehydration in cats (6). Kudo (7, 8) showed that in acute or chronic thirst there is a great loss of weight of the various organs of the body, which loss, however, is similar in magnitude to that due to starvation. His young rats showed a progressive tolerance to thirst, less fluid being required to keep the body weight constant. Jackson and Smith (9), in studies of growth curves of rats on restricted water and their restricted food controls, found that the restriction of water intake interferes with growth on its own account, as well as through food intake.

There are conflicting reports of the changes in the total water and electrolyte content of the body in dehydration. These differences are chiefly due to the various methods used to produce a state of dehydration experimentally. We have attempted to study the problem by noting the effects of sudden deprivation and also of diminishing intake of water on young rats. It has been reported by Marriott (1), Takai (10), Yamaoko (11) and one of us (12) that on a high protein diet, symptoms of severe dehydration are obtained more quickly and death occurs earlier. Therefore we employed a diet high in protein as well as a basal diet. The bodies of rats at various stages of dehydration were analyzed in order to see if any changes in water or mineral composition had taken place.

Experimental

Albino rats of Wistar Institute stock were weaned at twenty-one days of age and put on either the Basal Diet or the High Protein Diet. The sexes were separated and placed in cages having wire mesh bottoms so that the animals would not have access to their feces. Distilled water was given in calibrated bottles, and the daily intake noted. The food cups were weighed every day. When food was spilled, the tray under the mesh wire was taken out, the food separated from the feces and weighed, the amount being added to that of the uneaten food left in the cup. The animals were weighed every day, and their clinical condition noted.

The two diets used in these experiments (Table I) are modifications of Takai's diets (10). Both were found adequate for normal growth. The increment of growth curves of our rats on these diets fall within the accepted range for those for rats of the same age on Breeder's Diet which are subsequently used for Vitamin D assays in this laboratory. It will be noted that the Basal Diet and the High Protein Diet are nearly alike in caloric and mineral content, the main difference being the greatly increased nitrogen of the High Protein Diet.

After three weeks on these diets, the experimental period began. In the first experiment, twelve rats, forty-one to fifty days of age were used. Water was completely withdrawn, but the animals were allowed to eat as much food as they wished. Every other day, very small amounts of blood were collected by snipping the tails, and serum protein determinations were done by the refractometric method of Robertson (13), and the food intake, water intake and body weight were noted as before. The rats lost weight rapidly, their hair became ruffled, and they ate very little. Occasionally there was bleeding from the nose. Diarrhea was never present, but excretion of urine in all the rats was slight and showed traces of albumen. Eventually there was total anuria. The rats became weak and emaciated, and finally died, the survival time from the beginning of the experimental period being noted.

In the second experiment, water bottles were removed from the cages. For the first five days, one-fourth of the average daily intake

of water for the corresponding sex and diet, was given to each rat separately in a small glass castor. For the next five days, the water intake was cut to one-eighth, and after the tenth day, no drinking water was given at all. Again the serum proteins were followed, and the survival noted.

In the third experiment, three groups of eight rats each were used: two groups on the Basal Diet and the third on the High Protein Diet. The rats in the second Basal Diet group and those in the High Protein group were from four litters of closely related animals, the litters being equally distributed between the two groups. This was done in order to eliminate any differences that might be due to diverse heredities. The animals were fifty to fifty-five days of age at the start of the experiment, and the same procedure of diminishing water intake was followed. Animals in each group were killed by pairs at the beginning of the experiment, and on the fifth, the tenth and the twelfth days. The rats killed last were very near death. The following procedure was used: the rats were weighed and anesthetized with urethane. Then they were bled by severing the carotid artery, the blood being collected under oil. Immediately the intestines were excised, weighed, the intestinal contents removed, and the empty intestines reweighed. The weight of the intestinal contents plus that of any urine or feces lost during anesthetization, was subtracted from the live weight and the result called "net body weight". Calculations for total body composition were based on this figure. The rats meanwhile were skinned, and the liver, kidneys and lungs quickly removed and placed in tared bottles. The rest of the animal, with the empty intestinal tract added, was treated as a whole, and will be referred to as the "carcass." All organs and tissues were immediately weighed and frozen by placing in a freezing mixture of dry ice and acetone. The frozen carcass was ground in a meat grinder to insure better mixing and a larger surface for drying. The serum was centrifuged off, and weighed samples frozen. Then tissues and serum were dried in a vacuum dessicator placed in the freezing mixture, until water was completely removed. This took from eighteen to twenty-four hours, the tissues being weighed to a constant weight. This method was used for determination of water, for when tissues are dried in an oven, there is the possibility of autolysis which would give erroneous results. Total

fat was determined on the dried tissues by weighing them before and after ether extraction, using a continuous Soxhlet extractor. Since there are great individual variations in fat content, all further analyses were run and reported on dry, fat-free tissue, as this gives a much more accurate system of comparison. Next, the carcass, lungs, liver and kidneys were mixed together for analysis, as the separate organs were too small for accurate analyses determinations. The skin, however, was analyzed separately.

Total nitrogen by the Kjeldahl method and chlorine by the method of Sunderman and Williams (14) were run directly on samples of the dry, fat-free tissue. A third portion was ashed in quartz crucibles in a muffle furnace at 500°C, to a white ash, which was weighed and dissolved in normal hydrochloric acid and the volume brought up to one hundred cc. Further analyses were run on this ash solution. For sodium, the gravimetric method of Barber and Kolthoff (15) as modified by Butler and Tuthill (16) was used. Potassium determinations were run by Fiske and Litarczek's method (17) and phosphorus by the method of Fiske and Subbarow (18). These same methods were used in analyzing the diet ingredients, with the additional determinations of calcium by a modification of the Kramer-Tisdall method (19), magnesium by the method of Greenberg (20, 21), iron by the colorimetric procedure of Yoe (22) and sulphur by the classical method of precipitation as barium sulphate (23).

Results

The three weeks of pre-experimental observation showed no consistent difference in growth curves of rats on the two diets. However, the food intake figures show that both males and females on the High Protein Diet consistently ate less than those on the Basal Diet, and drank more water (Table II). The greatly increased protein content of the High Protein Diet would necessitate a larger amount of water in order to dissolve the excess urea excreted. Richter and Braily (24), using a different diet, give sixteen cc. as the daily water intake for females, and nineteen cc. for males at thirty days of age. They note that the water intake of rats increases in direct proportion with increase in body surface.

In the first experiment, where water was completely withdrawn, the serum proteins rose from the normal value of 6 to 7 gms. per hundred cc. serum to as high as 9.3. There was a definite rise in the serum proteins of each of the twelve rats studied, showing that the blood became more concentrated in sudden dehydration. Serum protein values for the rats on diminishing water intake, however, varied so much that no consistent trends could be followed.

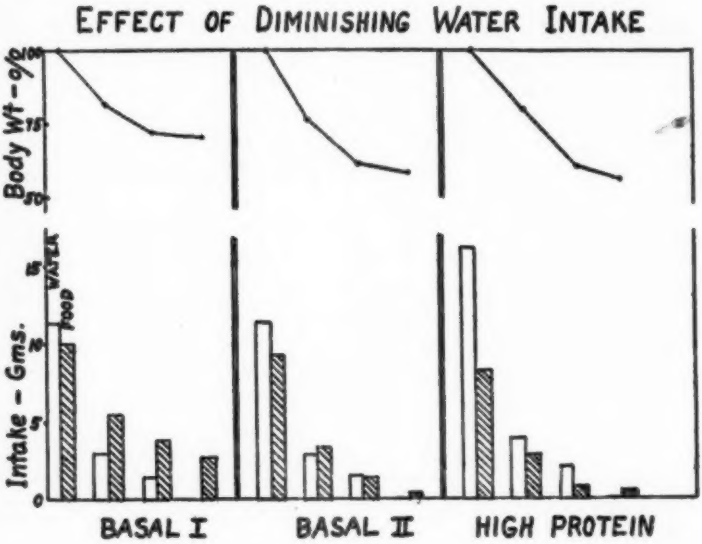

FIGURE I

Averages of eight rats for each diet group. The upper curves indicate percentage of original body weight. The amounts of food and water intake are expressed in gms. per rat per day, the four sets of columns representing (1) the control period, (2) five days on one-fourth the average daily water intake, (3) five days on one-eighth water intake and (4) two days without any water.

The survival time in both experiments showed clearly that the rats on the High Protein Diet were much more susceptible to decrease in water intake (Table III). Those on the Basal Diet lasted an average of 2.2 days longer after water was withdrawn than those

on the High Protein Diet. On diminishing water intake, the survival was 7.3 days longer for the Basal Diet rats. The high content of urea in the High Protein Diet seems to be a major factor in susceptibility to decreased water intake (12). This finding is in agreement with that of Takai (10) and Yamaoko (11).

As soon as water was diminished, the rats ate much less food, and the amount of diet eaten decreased parallel to the decrease in water (Figure I). This has been noted by Jackson and Smith (9) and others. It is an important factor, since it means that we are dealing with not only dehydration, but also with starvation. The loss of body weight, which became greater as the water intake decreased, is a striking result of dehydration and inanition. On the Basal Diet, the loss in the animals killed on the twelfth day was from 27 to 44 per cent of the original body weight, and on the High Protein Diet, from 41 to 46 per cent.

When the fresh weights of the organs of the animals were compared, it was found that the kidneys of the rats on the High Protein Diet were in all cases heavier than those on the Basal Diet (Table IV). This phenomenon has been reported by MacKay and MacKay (25, 26) who say that the demand put on the kidneys by increased nitrogen excretion only partially explains the hypertrophy. To test this, they fed a group of rats urea equal to that formed from the protein of their high protein diet, but the urea rats did not have increased kidney weight, so that the level of blood urea apparently is not a factor.

Analyses of the per cent of water in the various organs showed a surprising uniformity (Tables V, VI and VII). The only exception to this is serum, where the decreasing per cent of water in the Basal Diet groups shows concentration of the blood. Our figures for per cent water in the whole animals agree with normal values found in the literature (2). Of course a great deal of water was lost in the dehydrated, starved animals, and yet the composition of the tissues remained the same as that of the controls. It must be remembered that these figures include extracellular as well as intracellular water, so that any exchange between the two would not be apparent from the amounts of total water. However, the evidence remains that the organs and tissues are able to maintain the normal per cent of total water in spite of small water and food intake.

Fat (Table VIII) is known to vary greatly in individual animals. Our fat analyses again demonstrate this point, especially when per cent figures of dry tissue are compared. However, the total grams of fat per animal show clearly that a great amount of fat was lost, the amount increasing as the rats became more emaciated, until practically all the stored fat was gone. Since fat and glycogen are the first constituents to be burned in starvation, this loss cannot be attributed to dehydration alone.

Total ash (Table IX), expressed as per cent of dry, fat-free tissue, showed an increase as the animals became more dehydrated. The difference between the controls and those killed on the twelfth day was four per cent of the whole animal for the Basal Diet groups, and five per cent for the High Protein group. However, these figures are for whole body, and it must be remembered that the proportion of the skeleton to the soft tissues increased in the body of the emaciated animals as compared to the normal controls. This explains the apparent increase in ash.

Total nitrogen (Table X), expressed as mgs. per gm. of dry, fat-free tissue, remained constant throughout all groups. The body, although undoubtedly losing protein, is able to maintain its normal nitrogen composition even under conditions of extreme dehydration and starvation.

Since sodium and chlorine are the main ionic constituents of interstitial fluid, and potassium and phosphate the corresponding ions of the tissue cells, the amounts of these elements were determined in order to note any changes due to loss of water. Sodium (Table XI) showed a slight increase in each of the three groups, a 0.6 mg. per gm. increase of sodium in the whole body for the Basal Diet groups, and a 1.0 mg. per gm. increase for the High Protein group, comparing the rats killed on the twelfth day with the controls. This apparent increase, like that of ash, may be due to the increasing proportion of skeleton to the soft tissues as the rats became more dehydrated. Chlorine (Table XII) remained constant, so that the per cent composition of the extracellular fluid in the whole body seemed practically unchanged.

Turning to intracellular constituents, phosphorus (Table XIII) showed an increase of 7 mgs. per gm. of the whole body in all three groups, the difference being between the most severely de-

hydrated rats and the controls. It is possible that this increase also is only an apparent one due to the phosphorus in the skeleton. Potassium (Table XIV) showed a decrease of 1.0 mg. per gm. of the whole body in rats on the Basal Diet, and 2.2 mgs. per gm. decrease from the control figures in rats on the High Protein Diet. These trends of phosphorus and potassium, although consistent from group to group, are of a small order and in the opposite direction from each other, so that they do not appear to denote significant changes within the cells.

On the whole, it appears that, even after severe dehydration and starvation, the body is able to maintain practically the same percentage composition of tissues in respect to nitrogen, water and the electrolytes. This finding holds for the rats which were more susceptible to water deprivation, due to the High Protein Diet, as well as for those rats which survived longer on the Basal Diet.

Discussion

Whether the body is in the normal or dehydrated state, there is a continual exchange of salts and water between the plasma and the interstitial fluids, and between those fluids and the cells. It is believed that there is no change of permeability of the cells in dehydration. The membrane of the muscle cell seems to be impermeable to the sodium, potassium and chlorine ions, and makes adjustments entirely by transfers of water (27). For instance, if there is loss of potassium and retention of sodium, immediately water goes from the cells into the interstitial fluids so that the normal concentrations of potassium and sodium are maintained. The concentration of total water, however, remains constant, as we have shown.

A study was made by Hamilton and Schwartz (28) of the composition of tissues in dogs which were not given any water, but were fed by stomach tube. Under these conditions, more water was lost than base in muscle and skin. In the brain, liver and kidneys, the water withdrawn was not accompanied by a salt loss, so that there was an increase in concentration. This is a picture of true dehydration, unaccompanied by starvation, which accounts for the difference in results from other dehydration studies. In starvation alone, Gamble, Ross and Tisdall (29) found that the loss of fixed base was accompanied by loss of sufficient water to make an isotonic solution. This would indicate that the organism regulates the elec-

trolyte and water excretion in such a manner that the salt to water ratio of its fluids and their osmotic pressure are maintained at the normal level. Takai (10) and Drake, McKhann and Gamble (5) found a normal per cent of water in dehydrated animals which refused to eat. On the other hand, Jackson and Smith (9) found a slight decrease of per cent water in dehydrated and starved animals and in starved controls.

Darrow and Yannet (30, 31) used an entirely different technique in order to study dehydration. They injected large amounts of isotonic glucose solution into the peritoneal cavity of animals. Since approximately the same volume injected was later recovered, they assumed that the total body water remained the same. Salts went from the extracellular fluids into the glucose solution, until the concentration of the latter was nearly the same as that of the blood plasma. In this way a state of dehydration was produced, and symptoms of that condition, especially loss of appetite, appeared. There was a shift of extracellular water into the body cells producing dehydration of the extracellular fluids and hydration of the cells, but the total per cent of water remained the same. Loss of nitrogen, potassium and phosphorus also were in the same proportions that these elements exist in muscle. Eichelberger and Hastings (32), using the same technique, found a loss of water, sodium, and chlorine in muscle during the first two-and-a-half hours after the injection of hypotonic glucose solution. This does not contradict the findings of Darrow and Yannet, but rather amplifies their results, for at the end of four hours after the injections, there was a return of water to the tissues.

Our own conclusions, based on the results presented in this paper, confirm the work of those who find that in dehydration accompanied by starvation, the normal percentage of water and salts of the body is maintained. In other words, the loss of electrolytes and nitrogen is parallel to the loss of water.

NOTE: We are indebted to Mr. Frederic Kapp for making the fat determinations.

Summary

Albino rats at weaning were put on either a basal or a high protein diet for three weeks, and then dehydrated by either diminishing the water intake, or by withdrawing water entirely. In both treat-

ments, those animals on the basal diet survived longer than those on the high protein diet. When water was withdrawn completely, the serum proteins showed a definite rise. Rats were killed at various intervals on diminishing water intake, and their bodies analyzed for water, fat, ash, nitrogen, chlorine, sodium, potassium and phosphorus. The per cent of these elements in the whole body remained the same in the experimental animals as in the controls. These results indicate that loss of body water is accompanied by a parallel loss of salts and nitrogen when dehydration is complicated by starvation.

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TABLE I.

DIETS USED IN DEHYDRATION EXPERIMENTS

	Basal Diet	High Protein Diet
Whole Wheat	80.4 per cent	25.4 per cent
Crude Casein	10.0	65.0
*Osborn & Mendel's Salt Mixture	3.6	3.6
Brewer's Yeast	1.0	1.0
Cod Liver Oil	5.0	5.0
	100.0	100.0
Calories per gram	4.2	4.0

MINERAL CONTENT IN MG. ELEMENT PER GM. DIET

Diet	N	Na	K	Cl	P	Ca	Mg	S	Fe
Basal	28.66	1.53	8.91	2.19	6.78	3.85	0.69	1.54	.092
High Protein	94.00	1.45	7.48	2.55	8.82	6.12	0.53	2.15	.091

Also traces of Al, Mn, F and I in both diets.

TABLE II.

INTAKE FOR NORMAL RATS

Three Weeks Pre-Experimental Period

(Rats 21 days old at start)

	Basal Diet		High Protein Diet	
	Males	Females	Males	Females
No. of rats	19	11	10	13
Water cc./day/rat	12.5	11.7	15.4	16.6
Food gm./day/rat	10.4	8.1	8.3	7.6
Food cal./day/rat	42.8	34.0	33.2	30.4
Water cc./gm./food	1.2	1.4	1.8	2.1

* Osborn and Mendel, J. Biol. Chem., *32*:309 (1917).

TABLE III.

SURVIVAL TIME OF DEHYDRATED RATS

I. Survival after complete withdrawal of water

Basal Diet		High Protein Diet		
Rat No.	No. Days Survival	Rat No.	No. Days Survival	Difference
16	9	18	7	
17	11	19	8	
24	7	20	7	
25	8	21	6	
		22	5	
		23	5	
		26	7	
		27	7	
Average	8.7		6.5	2.2

II. Survival after diminishing water intake

94	23	102	17	
95	23	103	17	
96	21	104	16	
97	20	105	14	
98	26	106	15	
99	23	107	20	
100	24	108	13	
101	24	109	15	
Average	23.2		15.9	7.3

TABLE IV.

FRESH WEIGHTS OF KIDNEYS (IN GRAMS)

In Normal and Dehydrated Rats

Treatment	I Basal Diet	II Basal Diet	High Protein Diet
Control	1.1516	1.3341	1.7438
	1.4556	1.2501	1.6975
¼ water	1.0492	0.9163	1.3331
	1.1070	0.9992	1.4310
⅛ water	1.0091	0.7711	0.9252
	0.9192	0.8700	1.0208
0 water	0.6744	0.7164	1.0050
	0.7305	0.7636	0.9750

TABLE V.

WATER

In Fresh Tissues of Normal and Dehydrated Rats

Basal Diet—Group I

Rat	Treatment	Whole Animal	Carcass	Liver	Kidneys	Lungs	Skin	Serum
		Per Cent Water in Fresh Tissues						
54 ♂	Control	67.0	72.0	68.0	75.0	78.0	52.0	
58 ♂		66.5	72.4	69.4	72.7	76.5	48.8	92.0
56 ♂	¼ water	65.8	70.8	66.5	73.1	76.4	50.5	
57 ♂		65.8	70.5	67.4	71.9	76.6	52.0	90.2
59 ♂	⅛ water	67.1	71.7	67.7	72.2	76.8	53.6	
60 ♂		65.1	70.2	68.1	72.3	77.1	50.0	
62 ♀	0 water	66.1	70.3	67.3	73.2	76.1	51.2	
63 ♀		66.0	70.0	67.0	71.9	76.7	51.5	86.6

TABLE VI.

WATER

In Fresh Tissues of Normal and Dehydrated Rats

Basal Diet—Group II

Rat	Treatment	Whole Animal	Carcass	Liver	Kidneys	Lungs	Skin	Serum
		Per Cent Water in Fresh Tissues						
64 ♂	Control	63.1	67.9	67.9	72.8	77.9	47.1	
76 ♂		63.9	70.5	67.8	73.4	78.1	47.2	92.4
65 ♂	¼ water	61.1	66.3	66.5	72.4	75.6	46.5	
66 ♂		61.0	65.7	66.7	71.4	75.6	47.6	91.7
82 ♀	⅛ water	64.2	69.6	67.7	71.9	76.3	44.0	
77 ♂		64.7	68.7	68.2	75.2	76.7	49.3	88.0
78 ♀	0 water	64.4	68.3	69.0	74.2	75.2	50.4	
79 ♀		62.1	66.9	68.1	73.3	75.2	47.6	90.0

TABLE VII.

WATER

In Fresh Tissues of Normal and Dehydrated Rats

High Protein Diet

Per Cent Water in Fresh Tissues

Rat	Treatment	Whole Animal	Carcass	Liver	Kidneys	Lungs	Skin	Serum
70 ♂	Control	62.6	68.1	66.9	75.0	77.2	48.0	
83 ♂		64.7	70.6	66.5	73.4	78.3	51.8	87.6
71 ♂	¼ water	62.3	67.2	66.6	74.2	76.0	47.9	
72 ♂		61.7	66.7	65.9	73.9	76.7	48.5	91.2
83 ♂	⅛ water	64.0	67.8	67.9	73.2	76.6	47.8	
84 ♂		62.7	67.7	67.9	71.1	76.5	49.7	90.1
86 ♂	0 water	62.1	67.5	69.2	73.0	76.8	47.7	
87 ♂		65.0	69.3	68.4	73.0	76.4	51.6	92.0

TABLE VIII.

TOTAL FAT

In Whole Bodies of Normal and Dehydrated Rats

Treatment	I Basal Diet		II Basal Diet		High Protein Diet	
Control	10.6	25.0	24.1	43.6	11.7	28.3
	18.5	33.1	12.8	28.4	11.3	27.1
¼ water	7.6	21.3	12.7	28.9	9.7	28.9
	5.8	14.9	12.5	29.3	7.8	21.9
⅛ water	1.9	5.9	2.8	14.3	3.3	12.3
	4.3	13.6	2.2	11.1	2.9	10.5
0 water	1.5	6.9	0.7	3.5	2.6	10.1
	2.0	8.1	3.2	13.9	1.9	12.9

Note: Figures in first column under each diet are for total grams fat; figures in second column are for fat, percent of dry tissue.

TABLE IX.

TOTAL ASH

In Whole Bodies of Normal and Dehydrated Rats

	Per Cent Ash in Dry, Fat-Free Tissues		
Treatment	I Basal Diet	II Basal Diet	High Protein Diet
Control	12.6	11.6	11.6
	11.7	13.1	11.6
¼ water	13.6	14.0	14.1
	14.0	12.9	14.7
⅛ water	15.0	16.9	17.3
	14.6	16.5	16.8
0 water	17.3	17.7	18.7
	16.7	15.9	16.3

TABLE X.

TOTAL NITROGEN

In Whole Bodies of Normal and Dehydrated Rats

	Mgs. Per Gm. of Dry, Fat-Free Tissue		
Treatment	I Basal Diet	II Basal Diet	High Protein Diet
Control	121.5	121.3	127.5
	123.2	127.2	125.9
¼ water	126.0	125.1	124.1
	129.4	123.2	129.5
⅛ water	129.7	127.9	123.0
	128.6	128.7	129.9
0 water	130.3	125.7	128.2
	128.1	126.9	129.4

TABLE XI.

SODIUM

In Whole Bodies of Normal and Dehydrated Rats

	Mgs. Per Gm. of Dry, Fat-Free Tissue		
	I	II	High Protein
Treatment	Basal Diet	Basal Diet	Diet
Control	3.99	4.06	3.92
	4.04	4.32	4.31
¼ water	4.29	3.91	4.01
	4.64	3.88	4.54
⅛ water	4.87	4.58	4.46
	4.47	4.67	4.91
0 water	4.92	4.94	5.23
	4.70	4.64	5.03

TABLE XII

CHLORINE

In Whole Bodies of Normal and Dehydrated Rats

	Mgs. Per Gm. of Dry, Fat-Free Tissue		
	I	II	High Protein
Treatment	Basal Diet	Basal Diet	Diet
Control	4.86	4.80	4.72
	4.79	4.77	4.83
¼ water	5.11	4.65	4.55
	4.71	4.84	5.13
⅛ water	4.53	4.43	4.97
	4.85	5.55	5.22
0 water	4.96	5.04	5.49
	4.58	5.35	4.92

TABLE XIII.

PHOSPHORUS

In Whole Bodies of Normal and Dehydrated Rats

	Mgs. Per Gm. of Dry, Fat-Free Tissue		
Treatment	I Basal Diet	II Basal Diet	High Protein Diet
Control	25.27	21.38	26.76
	22.00	25.32	25.64
¼ water	25.61	25.73	25.64
	27.39	23.27	26.41
⅛ water	27.89	30.98	30.71
	27.15	28.97	29.56
0 water	32.10	32.31	33.96
	30.72	28.24	29.14

TABLE XIV.

POTASSIUM

In Whole Bodies of Normal and Dehydrated Rats

	Mgs. Per Gm. of Dry, Fat-Free Tissue		
Treatment	I Basal Diet	II Basal Diet	High Protein Diet
Control	10.43	9.83	10.32
	10.50	10.84	9.94
¼ water	9.81	8.66	9.34
	11.18	8.55	9.59
⅛ water	9.46	8.72	9.04
	9.29	10.67	8.57
0 water	9.76	8.44	7.48
	9.37	9.34	8.52

TULAREMIA

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Tularemia is the one disease which may be called a truly American one; it has been explored from beginning to end by American investigators. When tularemia was first recognized as a disease it was believed to occur only in rodent animals; however, it is now known to affect other animals as well as the human. It is an acute infectious disease caused by the Bacterium Tularense. Primarily it occurs in nature as a fatal bacteremia of over 20 kinds of wild life, especially wild rabbits and hares. Secondarily it is a disease of man, transmitted from rodents to man by the bite of an infected blood-sucking fly or tick, or by contamination of the hands or conjunctival sac with the internal organs or body fluids of infected rodents, flies, or ticks. Whether it is occurring with increasing frequency in man or whether it is just being recognized, is not certain, though we know that cases of human tularemia are being reported with increasing frequency.

The history of the development of our knowledge of tularemia is rather interesting, for it is a disease of recent birth. In 1907, Dr. Ancil Martin of Phoenix, Arizona, reported several cases of a new type of fever which he had observed in patients following the skinning and dressing of wild rabbits. Because he could find no record of such a disease in his medical treatise he called the disease "rabbit septicemia". For three years there were no further developments in the history of tularemia. Undoubtedly other cases were occurring but they evidently passed as "Flu" or some other better known form of fever. Then in 1910 in Southern California, the ground squirrels developed an epidemic which seemed destined to reduce their population by the thousands. This lead to an investigation by two Public Health Surgeons, Drs. G. C. McCoy and C. W. Chapin. They were able to isolate from the infected animals an heretofore undescribed species of bacteria. It was a small pleomorphic organism, Gram negative, non-motile, and non-spore-bearing, which they

named bacterium tularense after Tulare County, California, whence came the infected ground squirrels. Still no one thought of a possible connection between this disease of rodents and any illness in man. Reports of the early work of McCoy and Chapin indicate that two of their co-workers during their bacteriological studies developed a disease associated with glandular enlargement and febrile disturbance. Our present knowledge of tularemia would warrant the assumption that they had contracted the newly discovered rodent disease, though this was not verified at the time by animal inoculation. Since then, the occurrence of tularemia in the human has been positively demonstrated. Credit for this discovery has been given Dr. Derrick Vail, an oculist of Cincinnati, Ohio, who in 1913 observed a peculiar form of conjunctivitis which he could not at first diagnose, but which through the laboratory studies of Wherry and Lamb, he finally recognized as squirrel plague conjunctivitis, or conjunctivitis tularense. The bacillus tularense was isolated in pure culture from the conjunctiva by Wherry and the disease reproduced in the guinea pig by dropping an emulsion of pure culture into the cul-de-sac of the lower eye lid. This was not only the first case of tularemia of the conjunctiva reported, but it represents the first case of the disease occurring in the human, recognized and proven as such by clinical study and laboratory tests.

Obviously, tularemia is a secondary disease of man, to whom it is usually transmitted directly by hands which have been in contact with body fluids of diseased structures of infected animals. The disease may also be transmitted through an intermediary hos such as the horse fly, wood tick, flea, or red bug. In 1919 Dr. Edward Francis of the Public Health Service in Washington was sent to Utah to investigate a peculiar new disease variously known as deer-fly fever or tick fever. He found many patients who had been treated for various ailments, ulcers, blood poisoning, typhoid fever, but without effect. Nearly all described their illness as beginning with ulcers on the hands followed by swollen glands, pains in the back, headaches, chilliness, and fever. Nearly all gave history of handling jack rabbits just before their illness, a few with a history of having been bitten by deer-flies. With infinite care and patience Dr. Francis and his co-workers began to trace the connection between the jack-rabbits, the deerfly, and the sick. They captured

hundreds of deerflies and let them bite healthy rabbits. They drew blood from the patients sick with the disease and injected it into guinea pigs; the rabbits and guinea pigs died. Dissection showed the characteristic signs of the disease and the presence of Bacterium tularense. So the chain of evidence was completed and this new disease named Tularemia. Dr. Francis himself in the course of his experiments, contracted tularemia and suffered from all the symptoms he had been studying so carefully in others.

As soon as these investigations were published, reports of other cases began to come in. Human cases have since been recognized in forty-six of the United States and in the District of Columbia. The only states in which cases have not been recognized are Vermont and Connecticut. The disease was reported in Japan in 1925, in Russia in 1928, in Norway in 1929, in Canada in 1930, in Sweden in 1931, and in Austria in 1935.

Tularemia has been mildly prevalent in Arkansas at least since 1925. In that year a physician described but did not diagnose an infection in a patient who had killed a rabbit and finding upon skinning it that the liver was spotted and apparently diseased, cut the animal up and fed it to his dog. In so doing he ran a piece of bone into his finger. The finger developed an ulcer, glands in his arm became swollen and he was acutely ill for several weeks. In 1926 two cases were diagnosed in Little Rock housewives who cut their hands while dressing rabbits. Considerable publicity was given these cases because of the rarity of the disease and since then there have been approximately 50 cases a year reported in Arkansas. Undoubtedly there were many more which were not diagnosed as tularemia. The State Hygienic Laboratory have had reports of tularemia from nearly every county in the state. They give the following statistics for positive agglutination tests: 1927—13 cases; 1928—8 cases; 1929—8 cases; 1930—20 cases; 1931—27 cases; 1932—42 cases; 1933—42 cases; 1934—33 cases; 1935—20 cases; 1936—17 cases; 1937—43 cases; and 1938 for the first six months—61 cases. It is interesting to note the marked increase in positive cases in Arkansas this summer, with more positive cases resulting from tick bites than in any other summer. This may be due to better diagnoses however, rather than more tularemia, since the insect transmission of tularemia is a factor which is frequently overlooked.

Bacterium tularense is known to have reached man directly from over 20 sources. The cottontail rabbit, jack rabbit, and the show-shoe hare are the direct cause of nearly 90% of the human cases in the United States. It is estimated that about 1% of these animals are naturally infected. The disease is a bacteria among them and is spread from rabbit to rabbit principally by the rabbit tick, but also by other blood-sucking anthropods—ticks, lice, and fleas. The rabbit tick, louse and flea do not bite man, and therefore they are not a source of infection. Rabbits raised under domestic conditions in rabbitries and hutches, although highly susceptible, have not been found naturally infected, due probably to their freedom from ticks.

In man, four different clinical types have been noted.

1. The ulceroglandular types in which the primary lesion is a papule of the skin, later, an ulcer, and is accompanied by enlargement of the regional lymph glands.

2. The oculoglandular type in which the primary lesion is a conjunctivitis and is accompanied by enlargement of the regional lymph glands.

3. The glandular type in which there is no primary lesion at the site of infection, but there is a glandular enlargement of the regional lymph glands.

4. The typhoid type in which there is no primary lesion nor is there glandular enlargement. This type has occurred from eating improperly cooked rabbits that were infected.

The great majority of the cases are of the ulceroglandular type with most having dressed wild rabbits—some were bitten by horse flies principally these were from Utah and the surrounding states. Hunters, marketmen, housewives and others who dress rabbits with bare hands become infected. In the majority of cases, a wound of entry has been inflicted at the site of cutaneous infection, either at the time of infection or shortly before or after. These wounds consist of cuts, punctures, or scratches by fragments of shot-shattered rabbit bone or knife, nail, barbed wire, thorn, brier, burr or splinter of wood. Since the organism will penetrate the normal skin, a wound of entry is not necessary for infection. The incubation period varies from one to ten days, the average being 3½ days. The onset is sudden and is manifested by headaches, vomiting, chilliness, aching bodily pains, and fever. A few cases are ambulant

throughout. Within 48 hours after the onset, these patients complain of pain in the area of the lymph glands which drain the site of infection. Only the regional glands are involved. The primary skin lesion is usually single and becomes, successively, papule, ulcer, and scar; in about 50% of the cases, the glands suppurate. In the typhoid type—fever is the only outstanding symptom. Fever is present in all the types of tularemia and continues from two to three weeks. Weakness, loss of weight, recurring chills, sweats, and prostration are prominent symptoms. Illness lasts about three weeks and is followed by a slow convalescence, covering a period of 2 or 3 months. Most patients recover without any bad after effects, but about 5% die, especially if the case is complicated by pneumonia. Among the complications that have occurred are appendicitis, ascites, pleural effusion, meningitis, and mastitis of the mammary gland. The laboratory diagnosis of tularemia is made conclusive by obtaining agglutination of bacterium tularense with the patient's serum or by obtaining a culture of the organism from the patient's ulcer or lymph nodes following guinea pig inoculation, or by obtaining a positive skin reaction, using an antigen prepared by Dr. Foshay of Cincinnati for intradermal injection. There is a complete absence of agglutinins in the blood during the first week of illness, but they are always present at some time in the second week, reaching a titre of about 1:1280 in the 3rd week. Agglutinins persist in long recovered cases and have been demonstrated 24 years after onset. Cultures may be obtained on coagulated egg yolk or blood-glucose-cystine agar, from guinea pigs inoculated with material from the primary lesions, from lymph nodes or with blood taken in the first week of illness. In the animal inoculation, the guinea pig may be injected with blood from the patient, or with any suspicious material. In many cases, however, injection is not necessary, since rubbing the suspicious material on the shaved abdomen of the guinea pig will suffice to transmit the infection. The infected guinea pig will usually live from three to five days and the organism can be recovered from the spleen or body fluids.

The agglutination test is carried out in the following manner: Place several test tubes, about 10 by 100 mm., in a rack. Add 1 cc. of normal saline to each of the last six tubes. Place 1.8 cc. of saline and 0.2 cc. of the patient's serum in the first tube and mix well.

Transfer 1 cc. of the mixture from the first to the second tube. Repeat this procedure to the 6th tube. Discard 1 cc. of the mixture from the sixth tube. These dilutions correspond to 1:10, 1:20, 1:40, 1:80, 1:160, 1:320; the last tube is used as a control. Add 1 cc. of bacterial suspension to each tube—the suspension should contain about 2,000,000,000 organisms per cc. This doubles the dilutions which now range from 1:20 to 1:640. Shake the tubes well and incubate at 37° C. for 2 hours and let stand in the refrigeratory overnight. Laboratory hint: If you are in a hurry to see if the tularemia agglutination is positive, shake the rack for five minutes; some of the tubes will show agglutination immediately, except when the test is only positive in low dilution.

One who has recovered from an attack of tularemia need not fear a second attack, because he is then immune to the disease. There is no record of a second attack in many; nor is there a record of the transfer of the infection from man to man.

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BOOK REVIEW

RECENT ADVANCES IN MEDICINE: Clinical, Laboratory, Therapeutic; by G. E. Beaumont, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (Lond.), Physician to the Middlesex Hospital; Physician to the Hospital for Consumption and Diseases of the Chest, Brompton; Lecturer in Medicine, Middlesex Hospital Medical School; Sometime Radcliffe Travelling Fellow, University of Oxford and E. C. Dodds, M.V.O., D.Sc., Ph.D., M.D., F.R.C.P., Courtauld Professor of Biochemistry in the University of London; Director of Courtauld Institute of Biochemistry, Middlesex Hospital; Pathologist to the Royal National Orthopaedic Hospital. Ninth Edition with 42 Illustrations, 1939. P. Blakiston's Son & Co.; 1012 Walnut Street, Philadelphia, Pa. Price $5.00.

This ninth edition since 1924 represents the most recent advances in the clinical, laboratory and therapeutic aspects of medical practice. Numerous references at the end of each chapter attests to the thoroughness with which the literature has been reviewed.

A short chapter on the sulphanilimide drugs gives the structural formula and clinical indications for each. The vitamins are dealt with in a similar manner. In the chapter on the kidneys various renal function tests are described in detail and the practical application given for the surgical, obstetric and medical case. Urinary infections with the drug indicated in the treatment of each are discussed. The use of, indications for and disadvantages of the protamine insulins are given in the chapter on glycosuria and diabetes mellitus as well as the newer aspects of laboratory examinations and dietetic management of these two conditions. Both new and old methods of investigation of hepatic and gastric function are given in detail. The old not infrequently again becomes the new as is shown by the discussion of the early feeding of patients with ulcer complicated by hematemesis as described by Lenhartz in 1904. A lower mortality rate is claimed by some authors as the result of this early feeding regime. In the chapter on basal metabolism reasons

are given to account for marked errors in the determination of the rate; conditions are mentioned in which the B.M.R. is increased and in which it is decreased. Cardiac irregularities, the electrocardiograph and some cardio-therapeutic measures are discussed in the chapter on the cardiovascular system. With a minimum of theoretical controversy the known facts concerning the sex hormones and their clinical applications are given in a concise manner from seventy-three references to the world literature. Methods for the determination of susceptibility to scarlet fever and diphtheria, immunization and the treatment of carriers are given. One chapter is devoted to the various diagnostic procedures of the cerebrospinal fluid. A short discussion is given on the various types of anemia and their treatment, agranulocytosis and the technique and results of treatment with pentnucleotide and the significance of the sedimentation rate. The techniques for the various colorimetric and non-colorimetric analyses of both blood and urine are given.

The authors have used a great deal of care to give a workable description of each procedure and all techniques described were personally performed by one or the other of them. The book gives in brief but well written form the standard procedures and latest advances as collected from the recent work of both American and Continental authorities, coupled with the experiences of the authors in the practical application of the various procedures to large hospital practices.

NEWS AND ANNOUNCEMENTS

THE REGISTRY OF MEDICAL TECHNOLOGISTS A. S. C. P.

The regular semi-annual examinations of the Board of Registry were conducted throughout the United States, Hawaii, Canal Zone, Puerto Rico, and Canada on October 27, 1939. There were 491 applicants for the tests, which were conducted by 149 clinical pathologists.

The next semi-annual class will be held in the spring of 1940. Applicants should file their papers as soon as possible, and not later than March 1, 1940, if they wish to be included in this group.

A new list of approved training schools has been issued and will be sent upon request to those interested in training. Several new schools have been added. There is a marked interest on the part of universities and colleges regarding the establishment of training schools under their auspices. Over 19,000 high school vocational departments of the United States have been circularized with information concerning the proper training of future medical technologists. This has brought forth an avalanche of inquiries from heads of these departments as well as students in the high schools throughout the nation.

It has come to the attention of the Registry office that efforts are being renewed for the state licensing of technicians. The present programs apparently are sponsored by groups whose standards do not meet those of the Registry. We would urge all registered Medical Technologists to secure further details from the Registry on these matters if they find it necessary to help combat any efforts which would tend to drag our banners to a lower level. The loyal and continuous cooperation of all registered M. T.'s is essential if we are to continue in our purpose to keep the profeessional standards of the clinical laboratory personnel of the United States on the highest possible scientific status.

NATIONAL

The Board of Directors of the American Society of Medical Technologists wish to report their action concerning a change in the Articles of Incorporation, Article XIII Amendment to Articles of Incorporation, in order to comply with the Michigan State Laws for nonprofit corporations the Board was obliged to change the vote of the annual meeting of May, 1939, by substituting the words "majority of members entitled to voting privileges" for the words "two-thirds vote of the House of Delegates" in both divisions (a) and (b).

This Article now reads: "These articles may be amended (a) upon recommendation of a two-thirds vote of the Board of Directors and the concurrence therein within one year by a majority vote of the members entitled to voting privileges, after notice to the Society of the proposed submission of such amendment in the manner provided in the preceding article for notice of amendments to the by-laws; (b) by a majority vote of the members entitled to voting privileges after similar notice of the proposed submission of such amendment concurred in within one year by a two-thirds vote of the Board of Directors."

This change can be permanently official after a vote of the House of Delegates in June, 1940.

B. ELLIOTT, *Chairman, Board of Directors.*

The following committee appointments have been made for the fiscal year 1939-1940:

Reception and Registration Committee

Myra Effinger, Chairman, Altoona, Pa.
Nell Stockton, Birmingham, Ala.
Sr. Amalia Margaret Klopsteg, Fairbault, Minn.

Nominating Committee

Anna Falck, Chairman, Lancaster, Pa.
Sr. Mary Faustine Masanz, Fond du Lac, Wis.
Ida Reilly, Hampton, Va.
Rose Matthaei, Houston, Texas
Cora Louise Miller, Philadelphia, Pa.

Entertainment Committee

Marian Gianniny, Chairman, E. Lansdowne, Pa.
Margaret Clark, North Little Rock, Ark.
Phyllis Stanley, Newark, New Jersey
Gladys Eckfeldt, Newton, New Jersey

Publicity Committee

David Silcock, Chairman, Versailles, Ky.

Program Committee

Doris Bowman Griffiths, Utica, New York, Chairman
Harry Falconer, Sioux Falls, So. Dak.
Bula Mae Forcade, Calgary, Alberta, Canada
Elisabeth Cramer, Lexington, Ky.
Ann Snow, North Little Rock, Ark.

Local Arrangements Committee

Phyllis Stanley, Chairman, Newark, New Jersey

Sisters Reservations and Entertainment Committee

Sr. Mary Celeste Waynant, Chairman, Baltimore, Md.

Education and Research Committee

Rowena Johnson, Tulsa, Okla., Chairman
Faith Dravis, Ellensburg, Wash.
Margaret Wade Brown, Fulton, Mo.

Exhibits Committee

Evelyn Jardine, Hanover, New Hampshire
Dorothy Asher Meyer, Chicago, Ill.
Phyllis Stanley, Newark, New Jersey

Arkansas

The Arkansas Society of Medical Technologists held their second Convention on Sept. 23, 1939, at the University of Arkansas Medical School, Little Rock, Arkansas.

The following program was presented:

9:00 A. M.—Registration.

9:30 A. M.—"The Educational Needs of a Technologist", Dr. Stuart P. Cromer, Dean of University of Arkansas School of Medicine.

9:45 A. M.—President's Address—Mrs. Violetta Wakefield, Fort Smith.

10:00 A. M.—Short talks by the Chairman of each Departmental Scientific Exhibit.

10:30 A. M.—Study of Scientific Exhibits.

12:30 P. M.—Luncheon.

2:00 P. M.—"Why Do a Gastric Analysis?", Dr. J. S. Levy, Little Rock.

2:30 P. M.—"A Few Points on Sperm Studies", Dr. Charles R. Henry, Little Rock.

3:00 P. M.—"Normal Hematopoiesis", Dr. W. C. Langston, Little Rock, U. of A. School of Medicine.

7:30 P. M.—Banquet.

Illinois

NOTICE OF FUTURE MEETING

Seventh Annual Meeting of the Illinois Society of Clinical Laboratory Technicians in conjunction with Annual Autumn Meeting of the Society of Illinois Bacteriologists, Champaign-Urbana, November 10, 11, 1939.

Technician's program, Friday evening, Saturday morning; Bacteriologist's program Saturday evening, Innman Hotel. Illinois-Wisconsin football game (Dad's day program), Saturday afternoon.

Friday evening—ninner 6:30, Program 7:30, Burnham City Hospital, Champaign:

Technical and Mechanical Aspects of Basal Metabolism, Jessie K. Lex, Diagnostic Clinic of George Mason Parker, M.D., and George Mason Parker, M.D., Peoria.

The Technician's Concern with the Vitamins, A. G. Carter, Department of Biochemistry, University of Illinois, Urbana.

Red Cell Changes and Their Significance (Lantern Slides), Dr. Steven O. Schwartz, 104 South Michigan Ave., Chicago.

Saturday morning, Room 112, Chemistry Annex, University of Illinois, Urbana:

8:45—Business meeting and election of officers.

9:30—Malaria and the Technic of Thick Films, Dr. Walter C. Earle, Champaign-Urbana Public Health Service.

9:50—Blood Sedimentation Tests An Aid in Diagnosis, Dr. George Sexton, Monticello.

10:10—The Neufeld Test for Pneumococcus Typing: Some of the Difficulties Encountered in Its Use (Microscopic Demonstrations), George F. Forster, Illinois Department of Public Health, Springfield.

10:30—A Method for the Recognition of Blood Subgroups, A1, A2, A1B, A2B, Beatrice Toharsky, M.A., Mount Sinai Hospital, Chicago. Discussion and Demonstrations by Dr. Davidsohn, Mount Sinai.

11:15—The Registry and Its Relation to the Technicians, Dr. I. Davidsohn, Chicago, Member of Board of Registry.

Saturday evening:

Incidence, Pathogenicity, and Identification of Monilia Albicans, Dr. Lyngerd Wickerham, Department of Bacteriology, U. of Illinois, Urbana.

Studies on Oral Lactobacilli, Dr. R. W. Harrison, Department of Bacteriology, U. of Chicago, Chicago.

Personal Recollection of Dr. Burrill, and Bacteriology of His Time, Dr.. B. F. Hottes, Emeritis Professor of Botany, U. of Illinois, Urbana.

Wisconsin

The Wisconsin Association of Medical Technologists held its fourth annual convention on Saturday, October 14, at the Marquette University Medical Building, Milwaukee, with a very good representation of the Medical Technologists throughout the state present.

At the morning session, Dr. Edgar End, Physiology department, Marquette University, spoke on "Helium in Science and Medicine." Mr. Karl York, Crime Prevention Committee, Junior Chamber of Commerce, Milwaukee, entitled his subject, "Sober Is As Sober Does." "Cerebrospinal Fluid" was explained by Dr. L. J. Van Hecke, Pathology Department, Marquette University. There was an address of welcome by Mrs. Leila Carson, President of the Milwaukee district of the Wisconsin Association of Medical Technologists, host for this meeting, and a response by the President of the State Association, Sister M. Beruadette Cass, Janesville, followed.

Following the business meeting in the afternoon, there were demonstrations of medical laboratory technique, including the photolemeter, the rapid method of blood typing, the Laughlin precipitation test for syphilis, the Widal test, the Alcohol test, Pentose Crystals, a positive culture of tubercle bacillus, and the new chocolate agar for gonococcus.

Dr. Joseph M. King, Surgical Director of the Milwaukee County Hospital, was the guest speaker at the banquet, citing "Laboratory Aids in Surgical Diagnosis."

The following officers were elected for the ensuing year:

President—Esther Thierstein, Milwaukee; President-Elect—Louise Mead, Milwaukee; Vice-President—Isabelle Gallagher, Madison; Secretary—June McCay, Milwaukee; Treasurer—Margaret Foley, Milwaukee; Historian—Laura Bates, Madison; Sergeant-at-Arms—Sister M. Faustine Masanz, Fond du Lac; Directors—Ethel Liebl, Oshkosh, Marian Tuttle, Superior.

ABSTRACTS

THE PROPERTIES OF ANTIGENIC PREPARATIONS FROM B. MELITENSIS: II SEROLOGICAL PROPERTIES OF THE ANTIGENS: A. A. Miles and N. W. Pirie. Brit. Jr. Exp. Path., vol. 20, No. 2, April, '39, p. 109.

A study involving the physio-chemical characteristics of the two states of aggregation of the antigenic complex of Br. melitensis.

CLEARING AND STAINING TOTAL MOUNTS FOR BONE: S. Benzer. Biol. Rev., vol. 1, No. 1, Dec., '38, p. 8.

Comparison of three methods for preparation of gross specimens with the technique of one the author states gives a better visualization of bones in their true positions.

EXPERIMENTAL PRODUCTION OF NEUTROPENIA WITH AMINOPYRINE: E. M. Butt, A. M. Hoffman and S. N. Soll. Arch. Int. Med., vol. 64, No. 1, July, '39, p. 26.

A review of the literature with a study of blood and bone marrow findings of dogs following oral administration of aminopyrine. The bone marrow is reported aplastic.

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